

Worldwide Clinical Experience with Voriconazole

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Now in 2004 therapeutic options in the management of invasive fungal infections have been extended by voriconazole, a new representative of the azole family, and the echinocandins. Voriconazole exhibits broad-spectrum activity at concentrations of ≤ 1 mg/L similar to itraconazole and posaconazole against the more common fungal pathogens such as *Candida* species (including fluconazole resistant *C.krusei* and resistant strains of *C.glabrata* and *C.albicans*) and is fungicidal to *Aspergillus* species as well as to certain *Scedosporium* and *Fusarium* species. The drug also exhibits good activity against less common clinical isolates including *Acremonium*, *Alternaria*, and *Curvularia*, as well as against the dimorphic fungi and the dermatophyte *Sporothrix schenckii*. *Voriconazole* appears less active against zygomycetes, such as *Mucor spp.*

Amphotericin B was the drug of choice for all invasive fungal infections in severely ill patients for more than 30 years. It acts by increasing the permeability of the fungal cell membrane by binding to ergosterol components. The drug has a very narrow therapeutic index. The most serious toxic effect of amphotericin is nephrotoxicity as manifested by renal loss of potassium. The dose-dependent toxicity of amphotericin B was the rationale for binding amphotericin B to lipid carriers, aiming at an increased therapeutic index. Formal randomized comparisons with standard amphotericin B deoxycholate have never been made. Encouraging clinical data regarding the safety of lipid formulations of amphotericin B have been reported but studies on efficacy in proven invasive infections remain limited. Only one small randomized multicenter trial has shown possibly superior efficacy of 5 mg/kg/day liposomal amphotericin B when compared with 1 mg/kg/day amphotericin B deoxycholate in the treatment of neutropenic patients with either documented or suspected pulmonary aspergillosis.

Azoles are better tolerated and certainly constitute a suitable alternative to intravenous amphotericin B for many indications. They possess a more manageable spectrum of toxicity. Fluconazole and itraconazole have, therefore, become popular alternatives to amphotericin B for many serious fungal infections. An important limitation of these antifungal compounds is their propensity to interact with coadministered drugs. Moreover, increasing resistance of fungal organisms to fluconazole, especially the *Candida* species, may become a problem with indiscriminate

prescription of the safest of all antifungal drugs. In patients with chronic aspergillosis as well as in those who have been treated during acute phase with intravenous amphotericin B, itraconazole had become a frequently favored option. There are theoretical concerns about a possible antagonism between azoles and polyenes, but sequential use of the agents did not bear out this concern. In the largest randomized trial so far voriconazole, was compared with amphotericin B for primary therapy of invasive aspergillosis. Patients with definite or probable aspergillosis were randomized to receive amphotericin B deoxycholate (1 mg per kilogram per day; n=133) or intravenous voriconazole (6 mg per kilogram for two doses on day 1 then 4 mg per kilogram twice a day; n=144) followed by 200 mg twice a day orally. Other licensed antifungal treatments were allowed after failure or intolerance to initial randomized therapy. Underlying conditions were mainly allogeneic hematopoietic stem cell transplantation, acute leukemia or other hematological diseases. At week 12, successful outcome was seen in 52% voriconazole and 32% amphotericin B treated patients (95% confidence interval: 32.9% to 10.4%). Survival was 71% with voriconazole and 58% with amphotericin. Successful completion of the initially assigned regimen were observed in 54% and 22% respectively. Voriconazole treated patients experienced significantly fewer severe adverse events. It is evident that the new drug has to be considered the golden standard for treatment of aspergillosis anno 2003. It also demonstrated clinical efficacy against candidiasis and offers promise for the treatment of some hitherto notoriously difficult-to-treat rare infections such as *Scedosporium* and *Fusarium* species.